

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kohl et al.

Serial No.: 045,799 (Continuation of SN 748,591)

Filed: April 28, 1987

For: DIALKOXYPYRIDINES, PROCESSES FOR THEIR PREPARATION, THEIR
USE AND MEDICAMENTS CONTAINING THEM

Group Art Unit: 121

Examiner: Jane T. Fan

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

December 04, 1987

Sir:

DECLARATION UNDER RULE 132

I, UWE KRÜGER, declare and say:

THAT, I am the declarant of a Declaration under Rule 132 executed on April 24, 1987, and filed together with the above application on April 28, 1987.

THAT, in order to comply with items 1, 2 and 3 of the Official Action of September 01, 1987, which refer to said Declaration, the following explanations are made:

1. In the Declaration filed on April 24, 1987, it was said that it was the objective of the invention described and claimed in the above application, to improve the specificity - in order to decrease side effects - by reducing the reactivity at neutral pH down to a limit of pH 5, the stability in solution at pH 5 being an appropriate criterion for the selection of optimised structures which still should be sufficiently reactive at $\text{pH} < 2$ and highly active in $(\text{H}^+ - \text{K}^+)$ -ATPase inhibition. Careful investigations with several dozens of 2-(2-pyridylmethylsulfinyl)-benzimidazoles have shown that high potency alone is not a guarantee of therapeutic applicability. On the contrary, high potency often turned out to be attached to low specificity.

Thus, it was a sort of tightrope walk to find out by thorough investigations those compounds which were on one hand highly specific and on the other hand still sufficiently potent. The dialkoxypyridine compounds claimed in SN 045,799 meet these requirements in a perfect manner: In the Declaration of April 24, 1987, the high specificity of the Compounds of SN 045,799 was demonstrated, and in the accompanying Declaration under Rule 132 made by Konrad Heintze, which is based on comprehensive comparative tests, it is shown that the compounds of SN 045,799, USP 4,555,518 and USP 4,560,693 are approximately equal in potency.

When the stability data presented in Table 2 of the Declaration of April 24, 1987, are set against the data concerning the therapeutic mode of action (reduction of ulcer index) in Konrad Heintze's Declaration, the conclusions compiled in the following Table are substantiated:

Table

Activation at pH 5 and potency (ED_{50}) of Compounds of SN 045,799 as compared with Compounds of USP 4,555,518 and USP 4,560,693

Compound No.*	half-life (hours) at pH 5 (CH ₃ CN/buffer 1:3)	relative stability factors of (I) [half-life ratios (I)/(P)]	ED_{50} -Doses (μ mol/kg) for reducing the ulcer index by 50 %	relative potency factors of (I) [ED_{50} ratios (P)/(I)]
4 (P)	0.8	26,2	0.73	1,22
5 (I)	21		0.60	
12 (P)	2.1	10,0	0.93	0,86
14 (I)	21		1.08	
13 (P)	1.0	29,0	1.96	1,39
15 (I)	29		1.41	
17 (P)	1.4	7,1	1.48	1,06
18 (I)	10		1.40	
20 (P)	2.7	10,4	0.45	0,37
21 (I)	28		1.21	
24 (P)	3.6	22,2	0.50	0,49
25 (I)	80		1.01	
29 (P)	1.4	22,9	0.85	0,31
30 (I)	32		2.71	

*The compound numbers correspond to the compound numbers in the Declaration of April 24, 1987, and in Konrad Heintze's Declaration. (P) indicates a prior art compound, (I) indicates a compound according to the invention claimed in SN 045,799.

The data in the above Table clearly show that the compounds 5, 14, 15 and 18, which are more stable at pH 5, are simultaneously equally potent as compared with their structurally closest related counterparts 4, 12, 13 and 17, respectively. Due to the improved stability combined with equal potency, less side effects are to be expected. Thus it can be said that the claimed dialkoxy compound 5, 14, 15 and 18 (potency and side effects regarded simultaneously) are significantly superior to their alkoxy-alkyl counterparts.

The compounds 21, 25 and 30 are slightly less potent (by a factor of about 2 to 3) than their respective counterparts 20, 24 and 29, but the stability at pH 5 is improved by a factor of about 10 to 23. Therefore, it seems not to be justified to draw the conclusion that the greater dosage which is required will offset the advantage of less-side effect which is expected on account of the improved stability. Thus, also compounds 21, 25 and 30 are believed to be superior to their alkoxy-alkyl counterparts.

2. The compounds 1-3, 10, 19, 22 and 27 were included since the corresponding stability data, which had been compiled formerly, were regarded as additional proof for the general conclusion: dialkoxypyridine compounds are more stable than monoalkoxypyridine compounds.

3. Examiner's position that the comparison is still not commensurate with the scope of the generic claims is noted but not understood. The list of 30 compounds (18 prior art compounds and 12 claimed compounds) in the Declaration of April 24, 1987, (Table 2, page 7), clearly shows that - irrespective of the substituent(s) in the benzimidazole part of the molecule - in each pair of compounds **always** those compounds have a significant higher stability, which have two alkoxy groups in the pyridine part of the molecule instead of one. There is no reason to believe that this picture would change if e. g. R1 were chlorodifluoromethoxy instead of difluoromethoxy or if R1' were methyl instead of methoxy.

It is the inventors' special merit to have enlarged the stock of technical knowledge with the recognition of the fact that in the field of 2-pyridyl-methylsulfinyl-benzimidazoles those compounds with **two** alkoxy groups in the pyridine ring have stability characteristics which are unexpectedly superior to

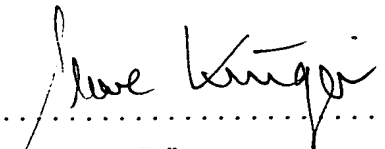
those of the compounds with only **one** alkoxy group in the pyridine ring. No reason is known to believe that the properties found for tested compounds with two alkoxy groups would not be possessed by any other claimed 2-pyridyl-methylsulfanyl-benzimidazole with two alkoxy groups in the pyridine ring.

THAT, in view of the comparative test data presented in Konrad Heintze's Declaration, and in view of the stability data, the significance of which has been explained in detail in the Declaration of April 24, 1987, it can be affirmed that the compounds of SN 045,799 are unexpectedly superior to the compounds of the closest prior art (USP 4,555,518 and USP 4,560,693).

THAT, it was not foreseeable that the compounds of SN 045,799 which have as an essential structural feature **two** alkoxy groups in the pyridine ring, would show a chemical stability which is so unambiguously superior over known compounds, having only **one** alkoxy group in the pyridine ring.

The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance, Federal Republic of Germany,
this 4th day of December, 1987.


.....
Dr. Uwe Krüger